Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy

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Abstract: BACKGROUND To report the primary endpoint of a randomized trial comparing pain response following palliative stereotactic body radiation therapy (SBRT) versus conventionally-fractionated 3D-conformal radiotherapy (3DCRT) for previously untreated spinal metastases. METHODS Fifty-five patients with histologically/radiologically confirmed painful spinal metastases were analyzed in this single-institutional, non-blinded, randomized explorative trial. Participants were randomly assigned (1:1) to receive single-fraction SBRT (24 Gy) or 3DCRT (30 Gy in 10 fractions). The primary endpoint was pain relief of >2 points on the visual analog scale (VAS) measured within the irradiated region at 3 months following radiotherapy completion. Other recorded parameters included pain response (per International Bone Consensus response definitions), use of concurrent medications and opioid usage (oral morphine equivalent dose, OMED). All parameters were assessed at baseline and at three and six months after RT. Intention-to-treat analysis was applied. This trial is registered with ClinicalTrials.gov, number NCT02358720. FINDINGS Despite no significant differences for VAS at 3 months between groups ($p = 0.13$), pain values decreased faster within this time period in the SBRT arm ($p = 0.01$). At 6 months following RT, significantly lower VAS values were reported in the SBRT group ($p = 0.002$). There were no differences in OMED consumption at 3 ($p = 0.761$) and 6 months ($p = 0.174$). There was a trend toward improved pain response in the SBRT arm at 3 months ($p = 0.057$), but significantly so after 6 months ($p = 0.003$). No patient in the SBRT group experienced grade 3 toxicities according to the Common Terminology Criteria for Adverse Events v.4.03. CONCLUSIONS This randomized trial demonstrates the utility of palliative SBRT for spinal metastases, which was associated with a quicker and improved pain response. Larger ongoing randomized studies will assist in further addressing these endpoints.

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Phase II randomised trial

Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy

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ABSTRACT

Background: To report the primary endpoint of a randomized trial comparing pain response following palliative stereotactic body radiation therapy (SBRT) versus conventionally-fractionated 3D-conformal radiotherapy (3DCRT) for previously untreated spinal metastases.

Methods: Fifty-five patients with histologically/radiologically confirmed painful spinal metastases were analyzed in this single-institutional, non-blinded, randomized explorative trial. Participants were randomly assigned (1:1) to receive single-fraction SBRT (24 Gy) or 3DCRT (30 Gy in 10 fractions). The primary endpoint was pain relief of >2 points on the visual analog scale (VAS) measured within the irradiated region at 3 months following radiotherapy completion. Other recorded parameters included pain response (per International Bone Consensus response definitions), use of concurrent medications and opioid usage (oral morphine equivalent dose, OMED). All parameters were assessed at baseline and at three and six months after RT. Intention-to-treat analysis was applied. This trial is registered with ClinicalTrials.gov, number NCT02358720.

Findings: Despite no significant differences for VAS at 3 months between groups ($p = 0.13$), pain values decreased faster within this time period in the SBRT arm ($p = 0.01$). At 6 months following RT, significantly lower VAS values were reported in the SBRT group ($p = 0.002$). There were no differences in OMED consumption at 3 ($p = 0.761$) and 6 months ($p = 0.174$). There was a trend toward improved pain response in the SBRT arm at 3 months ($p = 0.057$), but significantly so after 6 months ($p = 0.003$). No patient in the SBRT group experienced grade ≥ 3 toxicities according to the Common Terminology Criteria for Adverse Events v.4.03.

Conclusions: This randomized trial demonstrates the utility of palliative SBRT for spinal metastases, which was associated with a quicker and improved pain response. Larger ongoing randomized studies will assist in further addressing these endpoints.

Abbreviations: CR, complete response; CT, computed tomography; CTCAE, common terminology criteria for adverse events; CTV, clinical target volume; 3DCRT, conventional 3D conformal radiotherapy; EBRT, external body radiotherapy; Gy, gray; IMRT, intensity-modulated radiotherapy; IP, intermediate pain; MRI, magnetic resonance imaging; MV, megavolt; OAR, organ at risk; OMED, oral morphine equivalent dose; OS, overall survival; PP, pain progression; PR, Partial response; PTV, planning target volume; QoL, quality of life; RT, radiotherapy; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; VAS, visual analog scale; VMAT, volumetric modulated arc therapy.

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Approximately one third of cancer patients will develop bone metastases, approximately two thirds of which involve the vertebral column, most commonly at the thoracic and lumbar levels [1,2]. Conventionally fractionated 3D-conformal radiotherapy (3DCRT) is a well-recognized palliative treatment for painful bone metastases [3–14]. Comprehensive meta-analyses by Sze et al. and Wu et al. have provided consistent data regarding pain response after conventional external beam radiotherapy [13,14]. The overall (pain) response (OR) was up to 60% and complete (pain) response (CR) around one third [13,14]. A systematic review by Chow et al. yielded similar results in respect to OR, but lower CR rates of approximately 23% [3].

It has long been questioned whether an increase in radiation dose may lead to increased pain control while maintaining few toxicities. Although 3DCRT is limited in its capacity to dose-escalate owing to spinal cord dose constraints, stereotactic body radiation therapy (SBRT) is a highly conformal technique that does allow for safe dose-escalation [15–19]. These notions have been supported by phase I–II data demonstrating a clinical benefit of SBRT in the primary or salvage treatment of stable spinal lesions [20]. Phase II results of the RTOG 0631 study showed stereotactic radiosurgery to be feasible and accurate [21]. The latter is the basis for the currently ongoing RTOG 0631 phase III assessment, which aims to compare pain response and quality of life (QoL) between SBRT (single dose of 16 Gy) and EBRT (external beam radiotherapy) (single dose of 8 Gy).

To date, no randomized trials are available comparing SBRT with conventional 3DCRT in terms of pain relief. Furthermore, the interaction between ablative doses and pain response remains unclear. The aim of this randomized trial was to analyze pain response after high-dose SBRT versus conventional 3DCRT for this patient population.

Materials and methods

Subjects, recruitment strategy, and eligibility for enrollment

From November 2014 to March 2017, 60 patients with histologically confirmed cancer and painful bone metastases of the thoracic or lumbar vertebral column were randomized in both arms: high-dose single-fraction SBRT (24 Gy) versus standard fractioned 3DRT (10×3 Gy).

Inclusion criteria were ages 18–80, a Karnofsky performance score [22] $\geq$70, ability to provide written informed consent, a maximum of two irradiated vertebral bodies per region, a maximum of two different vertebral regions affected, and tumor distance >3 mm to the spinal cord. Exclusion criteria were subjects with significant neurological or psychiatric disorders precluding informed consent, previous RT to the given irradiation site, contraindications for MRI, multiple myeloma or lymphoma histology, or involvement of the cervical spine.

In total, five patients were duly excluded. Four patients in the SBRT arm had an insufficient distance between tumor and spinal cord. One participant from the control arm was excluded because of the confirmed diagnosis of multiple myeloma after randomization. 55 patients met the inclusion/exclusion criteria and were enrolled into the trial (Fig. 1).

The randomized trial, registered on clinicaltrials.gov (NCT02358720), was approved by the Heidelberg University Independent Ethics Committee (Nr. S-431/2013). Additionally, approval was given from the German Federal Office of Radiation Protection (BfS).

Design, randomized allocation, and procedures

This was a randomized, single-institutional, explorative study with the intention to compare pain response after high-dose single fraction SBRT versus conventional 3DCRT in patients with painful untreated spinal bone metastases. Details of the study design have been published previously [23]. A block randomization approach (block size of 6) was used to ensure that the two groups were balanced.

Two different techniques were evaluated on a 1:1 basis according to the randomization list: high-dose, single-fraction (24 Gy to the 80% isodose line) SBRT versus 30 Gy in 10 fractions of conventional radiotherapy.

The randomization procedure was carried out by a central office. Prior to their enrollment into the study, patients underwent staging of the vertebral column in connection with planning computed tomography (CT) and MRI to measure the spinal cord dimension. The prerequisite for participation in the study was the exclusion of spinal cord compression, along with a sufficient distance (>3 mm) between the metastasized vertebral body and spinal cord on MRI.

The primary endpoint-related parameters were measured at the start of RT (t_0), at the end of RT (t_1), 3 months post-RT (t_2), and 6 months post-RT (t_3). These parameters included the following: documentation of pain according to the Visual Analog Scale (VAS), neuropathic pain, OMED [5], and as well as individual patient-specific data such as use of concurrent medications.

During therapy, treating physicians documented each of these parameters; subsequently, patients continued complete documentation by means of pain diaries. VAS (collated as weekly mean values) and concurrent medication usage were documented daily for 3 months, and once after 6 months. In addition, use of basic pain medications and other concurrent medications (or medication changes) were continuously recorded from the start of RT to 6 months. In addition to patient-reported neuropathic pain use, opioid analgesic usage was converted into an oral morphine equivalent dose (OMED), and any non-opioid analgesics were also recorded.

Patient records were collected by the authors. The evaluation included all recorded data up to the 6-month follow-up interval. The baseline data of the patient characteristics are presented in summary (Table 1).

Assessment of the primary endpoints

The primary endpoint of this randomized, single-institutional, phase II trial was pain response after high-dose single-fraction SBRT versus conventional 3DCRT in patients with painful, previously untreated spinal metastases. The primary endpoint was defined as pain relief >2 points according to the visual analog scale (VAS) measured at the irradiated region three months after RT (t_2). The pain response was assessed according to the International Bone Consensus response categories by Chow et al. [5] as complete response (CR), partial response (PR), pain progression (PP), and intermediate pain (IP) at 3 and 6 months after RT. Complete response (CR) was defined as VAS = 0 after 3 months and partial response (PR) as an improvement by at least two score points after 3 and 6 months. CR was defined as VAS = 0 at the treated site with no concurrent increase in analgesic intake (stable or reducing analgesics in daily OMED). PR was defined as pain reduction of 2 or more at the treated site without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain. PP was defined as increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline. Any response not covered by the complete response, partial response, or pain progression definitions was called "intermediate pain". Responders were defined as having CR or PR, non-responders as having PP or IP.

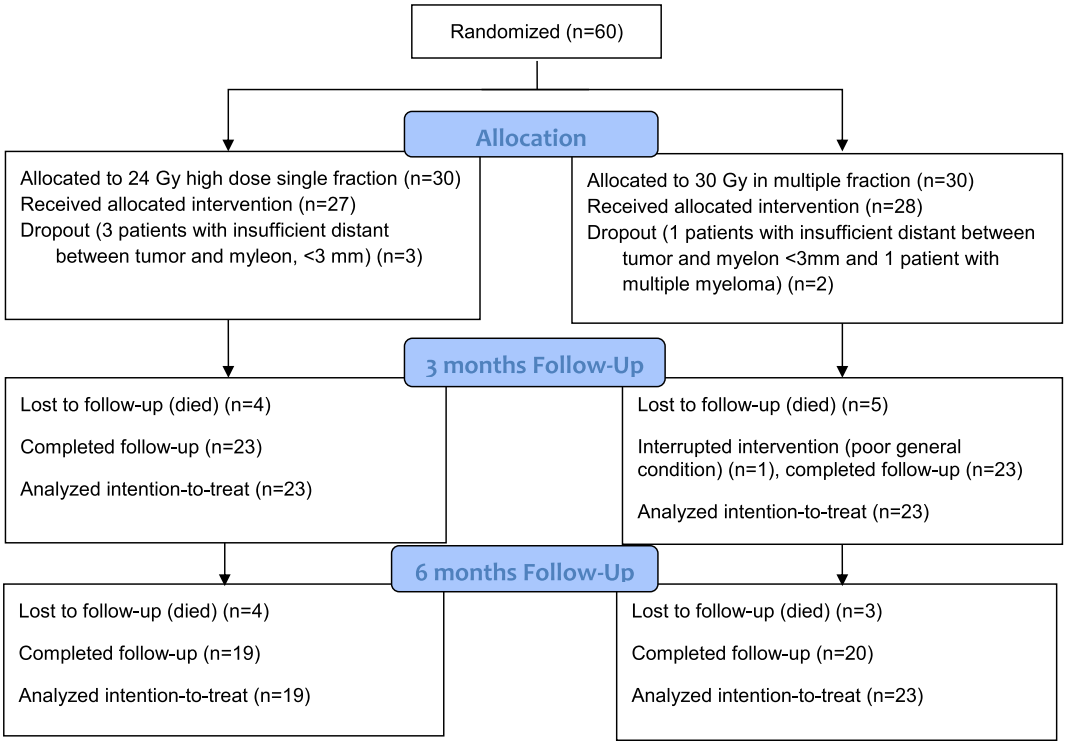

Fig. 1. Trial profile.

Radiotherapy

CT simulation was carried out with custom immobilization using Aquaplast® head masks, vacuum mattresses, and/or Wingstep® arm abduction framework. Regarding target delineation (performed with MRI co-registration), each vertebral body was divided into 3 sectors. Sectors I and III represent the lateral area of the vertebral body with the respective ipsilateral left or right pedicle, lamina, and transverse process. Sector II represents the middle third of the vertebral body with the spinous process. The gross tumor volume (GTV) was defined as the visible lesion with a 3 mm safety margin. The CTV included the affected vertebral body sector/s plus any unaffected sector. The PTV was defined by adding a 5 mm safety margin to the CTV. The volume (PRV) of the planning organ at risk (OAR), in this case the spinal cord, was a 3 mm expansion of this structure. The margin to the spinal cord was never less than 3 mm. The PTV never overlapped with the spinal cord or cauda equina.

In the SBRT cohort, the planning target volume (PTV) was to be covered by the 80% isodose line, and a single fraction of 24 Gy was prescribed to this isodose line. OAR tolerance doses were per the RTOG 0631 trial [24]. SBRT was delivered by an Elekta Versa HD linac employing MLC Agility leafs and a width of 5 mm at isocenter distance, with full dual VMAT arcs (178°–182° ccw, 182°–178° cw). Treatment was delivered using one of three possible techniques. VMAT with 6 MV flattering filter free (FFF) beams was delivered at a dose rate of 1400 MU/min. TomoTherapy (Accuray Inc., Madison, WI) was another technique; image guidance thereof comprised of pre-treatment megavoltage CT, followed by delivery of 12 Gy, followed by repeat megavoltage CT, and delivery of the remaining 12 Gy. The third technique was step-and-shoot IMRT with flattened 6 MV photons. Dose delivery and dosimetric accuracy of each plan were assessed by patient specific quality assurance (QA) using 3D-reconstucted dose measurement with the OD1500 2D-detector array inside the OCTAVIUS 4D rotational phantom.

For the 3DCRT arm, treatment was performed as irradiation of the involved vertebral body as well those immediately above and below to a total dose of 30 Gy in 10 fractions, most commonly delivered with 3 or 4 anteroposterior/posteroanterior beams. The same tolerance doses of the organs at risk as in the RTOG 0631 study are used [24]. Position verification was carried out weekly before radiotherapy by kilovoltage cone-beam CT (kV-CBCT) and before each fraction by orthogonal portal images being compared with digitally reconstructed radiographs (DRR) from the planning CT.

Statistical analysis

Owing to the exploratory nature of this study, a complete power calculation was not possible; however, with 30 patients in each group, it was possible to detect a standardized mean-value effect of 0.8 with 80% power at a significance level of 0.05.

All variables were analyzed descriptively by tabulation of the measures of the empirical distributions. According to the scale level of the variables, means and standard deviations or absolute and relative frequencies, respectively, were reported. Additionally, for variables with longitudinal measurements, the time courses of individual patients and are summarized by treatment groups. Descriptive *p*-values of the corresponding statistical tests comparing the treatment groups were given. The VAS was adjusted for concurrent medication. Analysis of covariance (ANOVA) with repeated measurements, with treatment group as a factor, and pain medication as a covariate, were done. The Wilcoxon signed-rank test was used to detect possible differences between groups after 3 and 6 months. Graphical visualization includes boxplots and mean course over time. Finally, we compared the groups for overall and bone survival, using Kaplan–Meier estimates and log-rank tests. Overall survival (OS) was defined as time from randomization until death, or censored at last contact.

Table 1
Demographics.

	SBRT group $n = 27$		3DCRT group $n = 28$		p-Value
	n	%	n	%	
Age (years)					
Mean (SD)	61 (8,2)		63,9 (10,8)		0,225
Gender					
Male	15	55,6	13	46,4	0,499
Female	12	44,4	15	53,6	
Weight (kg, SD)	76 (19,2)		78,2 (16,4)		
Height (cm, SD)	171,1 (8,5)		172,3 (8,7)		
Body mass index (BMI)					
Mean (SD)	25,8 (5,8)		26,5 (5,7)		0,899
Primary site					
Lung cancer	9	33,3	10	35,7	
Breast cancer	7	26,3	10	35,7	
Renal cancer	2	7,4	2	7,1	
Other	9	33,3	6	21,4	
Localization metastases					0,317
Thoracic	14	51,9	19	67,9	
Lumbar	13	48,1	8	28,6	
Number metastases					0,301
1 metastase	24	88,9	22	78,6	
2 metastases	3	11,1	6	21,4	
Distant metastases at baseline					
Visceral	12	44,4	14	51,9	0,586
Lung	11	40,7	4	14,8	0,033
Brain	7	25,9	3	11,1	0,161
Tissue	5	18,5	4	14,8	0,715
Hormonetherapy	6	22,2	8	28,6	0,589
Immunotherapy	8	29,6	8	28,6	0,931
Chemotherapy	11	40,7	13	46,4	0,671
Surgery	8	29,6	10	35,7	0,631
Neurological deficit at baseline	0	0	1	3,6	0,322
Bisphosphonate at baseline	11	40,7	13	46,4	0,671
Orthopedic corset at baseline	3	11,1	6	21,4	0,301
Medication at baseline					
Sleeping medication	1	3,7	1	3,6	0,979
Psychiatric medication	3	11,1	5	17,9	0,478
Opiate	11	40,7	10	35,7	0,701
NSAID	15	55,6	15	53,6	0,883

All statistical analyses were done using SAS software Version 9.4 or higher (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics were balanced between the two treatment arms (Table 1). The mean follow-up was 8.1 months for both groups. At baseline, NSAIDs were taken by 55.6% ($n = 15$) in the SBRT group, and opioid analgesics by 40.7% ($n = 7$). Corresponding numbers in the 3DCRT group were 53.6% ($n = 15$) and 35.7% ($n = 10$), respectively.

All surviving patients completed every required questionnaire. Four patients (14.8%) in the SBRT group died within 12 weeks of RT, and another 4 patients (14.8%) died of disease between 12 and 24 weeks. In the 3DCRT arm, 5 patients (17.9%) died within 3 months, and another 3 patients (10.7%) died between 3 and 6 months of RT (Fig. 1). No differences were present between groups in terms of OS ($p = 0.659$) and bone survival (BS) ($p = 0.660$) (Figs. 2–3). The mean OS was 7.9 months for both groups.

There were no significant differences in the pattern of recorded OMED consumption between treatment arms within 3 months (t_2) ($p = 0.761$) and 6 months (t_3) after RT ($p = 0.174$) (Fig. 4).

Twenty-three (85%) participants in the SBRT group and 23 (82%) in the 3DCRT group were assessable for pain response at 3 months. Nineteen (70%) patients in the SBRT arm and 20 (71%) in the 3DCRT arm were assessable for pain relief response at 6 months. The measurement repetition for variance analysis showed no significant difference in final VAS at 3 months (t_2) ($p = 0.13$). However, a difference in time to subjective pain relief between both groups during the first 3 months was noted ($p < 0.001$, Fig. 5). The VAS value decreased faster in the SBRT arm ($p = 0.01$, Fig. 6). At 6 months (t_3) following RT, significantly lower VAS values were reported in the SBRT group ($p = 0.002$). No differences were discerned between groups in terms of neuropathic pain at baseline, as well as 3 and 6 months following RT (Table 2).

Pain response is given in Table 3. At 3 months, there was a trend ($p = 0.057$) toward improved pain response in the SBRT group, as 43.5% therein experienced a CR, as compared to 17.4% in the 3DCRT group. IP was present in 21.7% of the SBRT cohort, as compared to 52.2% in the 3DCRT arm. At 6 months, 52.6% of the SBRT arm achieved CR (10.0% for 3DCRT), with IP figures of 15.8% versus 65.0%, respectively ($p = 0.003$). At this time period, 73.7% of the SBRT patients were categorized as responders, as compared to just 35.0% of those undergoing 3DCRT ($p = 0.015$).

RT was altogether tolerated well. No patient in the SBRT group experienced grade $\geq$3 acute or late toxicities according to the Common Terminology Criteria for Adverse Events (v.4.03). In the SBRT group, the most common acute side effect was fatigue (two cases

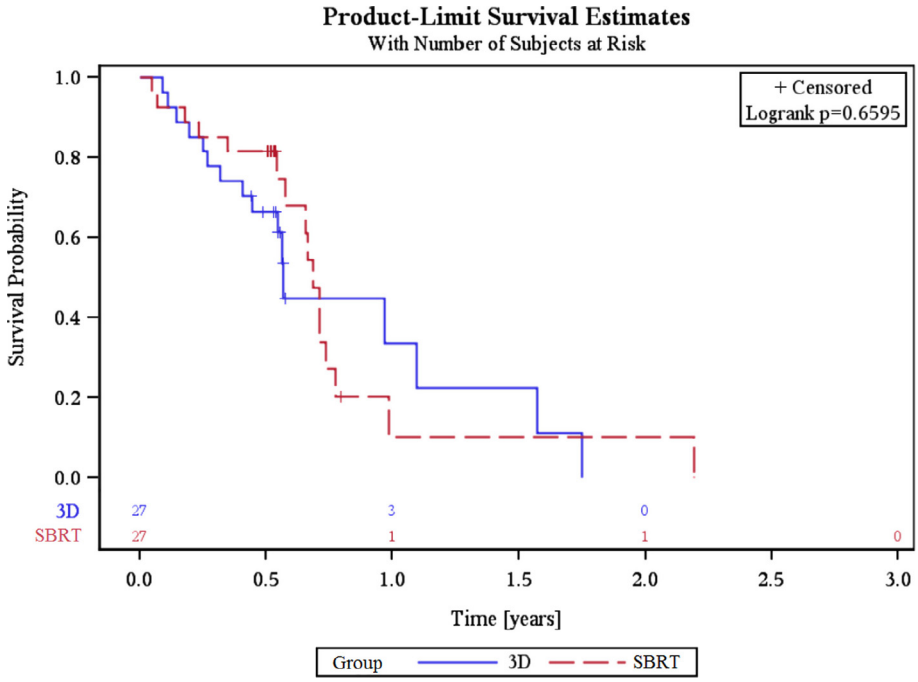

Fig. 2. Overall survival of both arms.

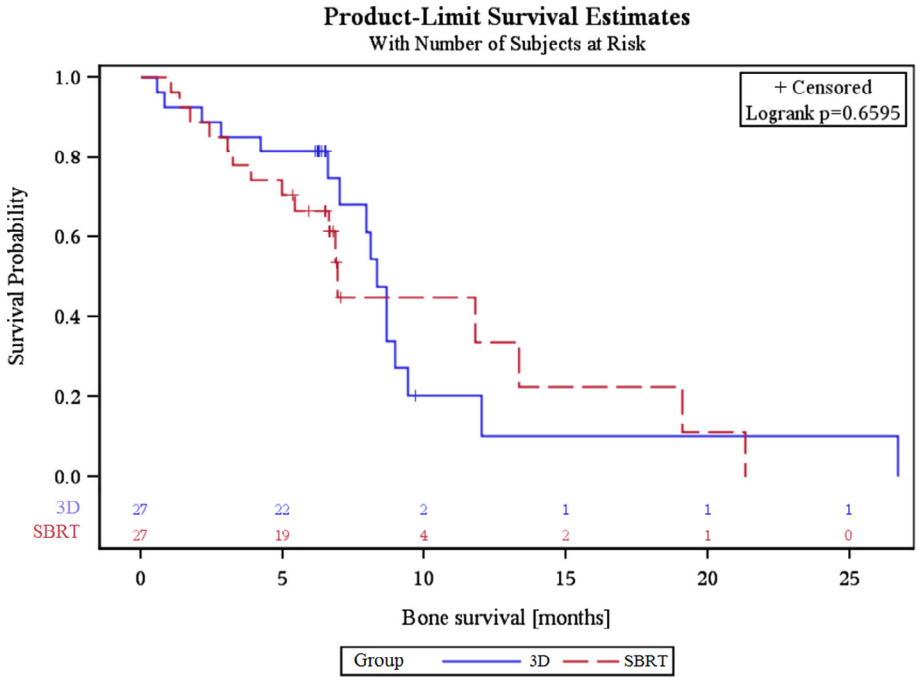

Fig. 3. Bone survival of both arms.

of grade 2, three cases of grade 1). One patient developed grade 1 dermatitis and another developed grade 1 dysphagia; two patients reported in-field pain flares for the initial 1–2 days. In the 3DCRT group, the most common acute side effect was fatigue (two cases of grade 2, five cases of grade 1). Five participants had grade 1 dermatitis, three patients had dysphagia (one of which was grade 2), and one patient reported grade 2 emesis (Table 4). No cases of radiation-related myelopathy or cauda equina injury occurred (Table 5).

Discussion

It is imperative to provide randomized evidence supporting the utility of advanced technologies in the palliative setting. This study compared pain responses between high-dose SBRT versus standard 3DCRT in the palliative setting for untreated spinal metastases without spinal cord compression. It was demonstrated that single-fraction SBRT reduced pain levels faster during the 3 months following RT ($p < 0.001$) and led to improved pain scores.

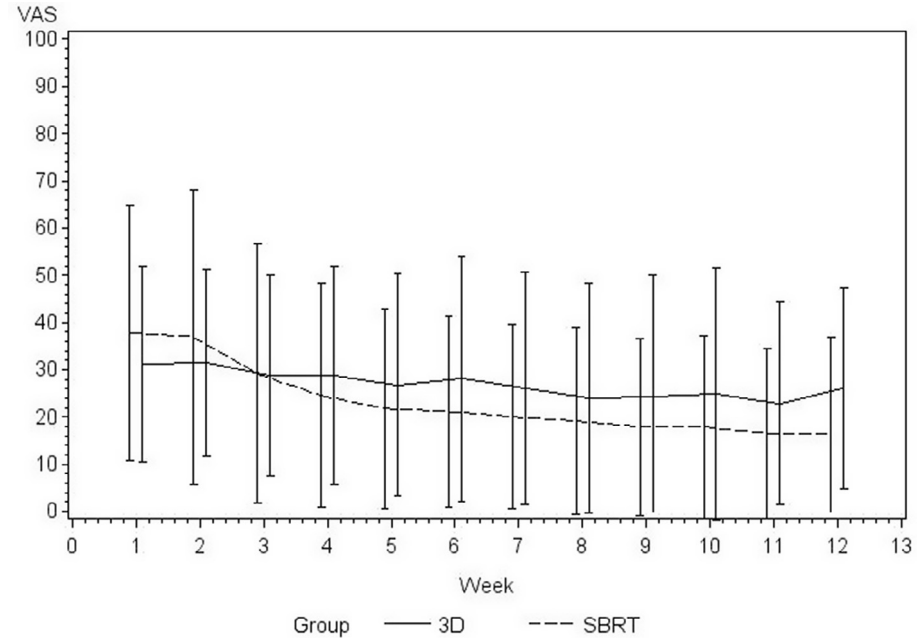

Fig. 4. VAS-value in both groups during 12 weeks after end of the radiotherapy.

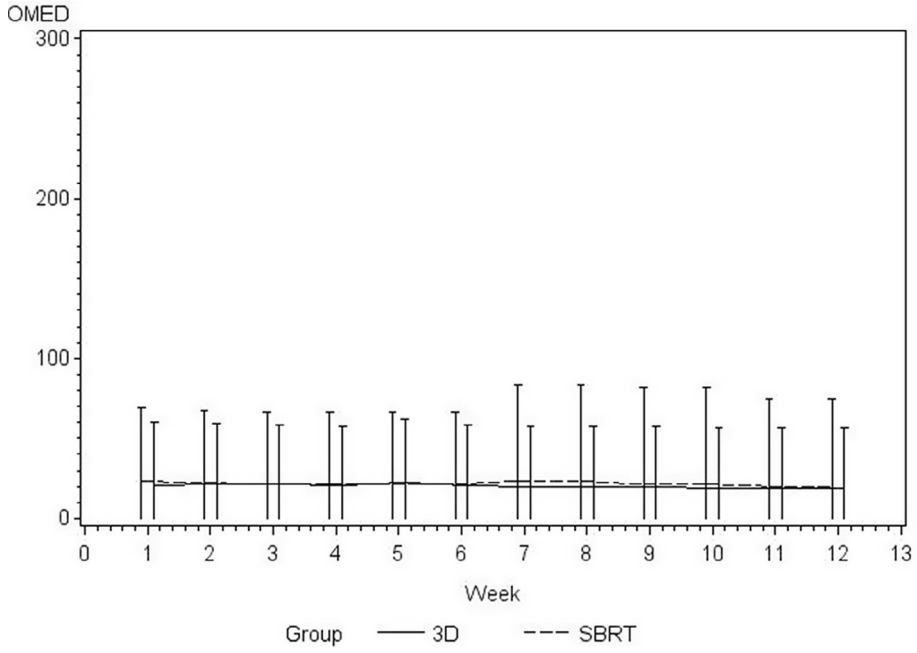

Fig. 5. OMED consumption in both groups during 12 weeks after end of the radiotherapy.

The hypothesis that ablative dosing leads to improved tumor control is not new. The application of higher biological doses was preferred for radioresistant tumors, those previously irradiated, and oligometastatic disease [9,16,25]. Experiences with single-fraction SBRT (24 Gy) is limited to a few datasets. Gerszten et al. illustrated its safety and efficiency using the CyberKnife technique in patients with advanced melanoma [25]. In this study, 23 of 28 consecutive patients had been previously irradiated at the involved spine level. The median follow-up was 13 months, and long-term improvement in pain relief was reported in 96% of patients (n = 27). The initial and post-treatment pain value was measured on a ten-point scale. Changes in analgesic dosages were not specified in detail [25].

The prospective non-randomized study by Nguyen and colleagues reported CRs after 3 and 6 months in 48.7% and 52.8% of 48 evaluable renal carcinoma patients [26]. The median follow up was 13.1 months, although only 8 metastases were treated with 24 Gy. Nevertheless, these results are comparable to our CR rates at 3 and 6 months with 43.5% and 52.6%. Another prospective non-randomized study demonstrated actuarial local control rates of 91.2% at 1 year in patients without prior radiation [27]. Like the prior study, a minority of patient received the same dose as in this trial, and no information was given regarding the pain response [27]. Nevertheless, these numbers line up well with another investigation displaying 90% actuarial local control in 93 patients with 103 spinal lesions. Although most patients in that study received

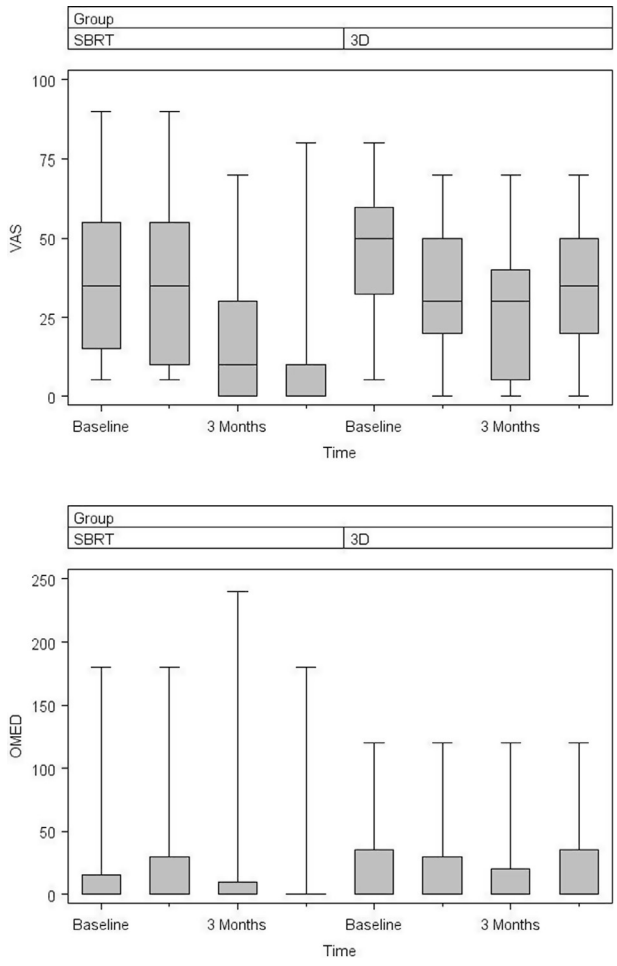

Fig. 6. OMED and VAS of both groups at measured points.

the same dosage as this trial, no information about the pain palliation was given [16]. Lastly, as this and most studies cannot completely address late toxicities, Moussazadeh et al. reported excellent toxicity profiles in highly selected survivors with a median follow up of 6.1 years [28].

The retrospective study by Jhaveri et al. investigated a dose–response relationship for time to pain relief in 18 renal cancer patients with 24 various bone lesions [29]. Two hypofractionated schedules were used 5×8 Gy and 3×8 Gy. The median follow up was 38 weeks. Pain relief was recorded in 78% of all participants. Whereby the pain relief was quicker and more durable in patient cohort treated with BED >/= 85 Gy. Only 14 patients were treated with spine lesions [30]. Nevertheless these results are in many respects comparable to ours. We achieved a similar responder rate of 73.7% after 6 months. In contrast, our study included patients with radiosensitive and radioresistant primary site. A different pain response of the various cancer could distort the results. Similar with our results, SBRT had no effect on changes in concomitant analgesic consumption [29].

The preexisting pathological fracture rate in our study was 29%. The incidence of new pathological fractures at 3 and 6 months following SBRT in our trial was 8.7% ($n = 2$) and 27.8% ($n = 5$) respectively. A systematic review by Faruqi et al. discerned risk factors for VCF after high dose SBRT, such as lytic lesions, preexisting VCF, and higher dose per fraction [30]. These factors were also

Table 3
Response according to Brief Pain Inventory score at 3 and 6 months in the per-protocol cohort.

	Intervention group $n = 27$		Control group $n = 28$		
After 3 months	*n*	%	*n*	%	*p*-Value
CR	10	43,5	4	17,4	0,0568
PR	6	26,1	7	30,43	
PP	2	8,7	0	0	
IP	5	21,7	12	52,2	
Responders	16	69,6	11	47,8	0,1343
Non-responders	7	30,4	12	52,2	
After 6 months					
CR	10	52,6	2	10	0,0034
PR	4	21,1	5	25	
PP	2	10,5	0	0	
IP	3	15,8	13	65	
Responders	14	73,7	7	35	0,0154
Non-responders	5	26,3	13	65	

Table 4
Acute side effects of both groups.

	Intervention group $n = 27$		Control group $n = 28$	
	Grad 1	Grad 2	Grad 1	Grad 2
Dysphagia	1	0	2	1
Emesis	0	0	0	1
Fatigue	3	2	5	2
Radiodermatitis	1	0	5	0

Table 2
Change in VAS-value, neuropathic pain and OMED.

	SBRT group $n = 27$			3DCRT group $n = 28$			
OMED	*n*	Mean	SD	*n*	Mean	SD	*p*-Value
Baseline (t0)	27	21.7	46.3	28	22.1	40.4	0.983
RT completed (t1)	27	23.1	46.3	27	20.7	39.3	0.825
After 3 months (t2)	23	20	54.6	23	18.7	38.1	0.761
After 6 months (t3)	19	13.4	41.5	20	27	43.5	0.174
Visual analog scale							
Baseline (t0)	27	38.7	26.2	28	46.4	22.2	0.253
RT completed (t1)	27	37.8	27	27	31.1	20.7	0.409
After 3 months (t2)	23	16.3	20.7	23	26.1	21.4	0.077
After 6 months (t3)	19	13.7	25	20	35	21.4	0.0024
Neuropathic pain							
Baseline (t0)	27	0.1	0.3	28	0	0.2	0.549
RT completed (t1)	27	0	0.2	27	0	0.2	1.000
After 3 months (t2)	23	0	0	23	0	0.2	0.339
After 6 months (t3)	19	0.1	0.2	20	0.1	0.2	1.000

Table 5
Treatment characteristics of both groups.

Spinal cord Dmax (Gy)	Mean	SD	Min	Median	Max
Intervention group $n = 27$	9,91	3,63	0,8	9,77	13,23
Control group $n = 28$	20,4	14,3	3	30,8	32,2

individually identified by other authors; VCF rates in those studies varied between 7% and 39% [31–35]. Our study showed a moderate pathological fracture rate in the SBRT arm, although the small sample sizes may have influenced this figure. No pathological fractures in either group required salvage surgical intervention.

There are a few limitations of this study worth mentioning, in addition to the aforementioned small sample sizes, the single-center nature, and shorter follow-up. First, studies of palliation encompass inherently heterogeneous patients, and the effect on subgroups cannot be analyzed. This also makes the results difficult to extrapolate to other work, along with the fact that the particular assessment methods (e.g., VAS) and frequencies thereof may differ from other work, thus also limiting generalizability.

Second, the Chow criteria recommend that patients with a pain level of minimum 2 (or rather 50/100) VAS be included in clinical trials. We included a total of 11 patients with a VAS <20/100, which is a constraint. This criteria also endorse utilization of the worst pain score over the previous 3 days, rather than the weekly mean values measured herein; these may also limit applicability. Third, steroid doses were not accounted for, which may be associated with pain levels and whether patients experienced "pain flares". Lastly, particular reasons for opioid utilization as well as subjective response of pain relief are inherently difficult to evaluate and are known limitations of any palliative study despite the prospective nature.

Salient points from our results indicate that ablative dosing to vertebral metastases may offer clear advantages in terms of durable pain response and rapidity of such. Although 3DCRT remains the standard of care, and economic considerations of advanced technologies for palliation remain a concern. The currently closed phase III RTOG 0631 study and the Canadian Cancer Trial Group SC24 phase II/III study (NCT02512965) have implications on the standard treatment well as its perceived cost-effectiveness.

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Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

HR and JD developed and planned this trial. TB is responsible for statistical considerations. TS, VV, RF, IS, NHN, TB, SEW and HR performed the examinations and RT supervisions. ET performed the treatment planning. HR and TS made the data collection. All authors read and approved the final manuscript.

Research in context

Evidence before this study

Narrative literature overview using the terms "SBRT", "spinal metastases" resulted in various single-arm prospective and retrospective work, which are summarized in the study protocol.

Added value of this study

This study compared the pain response between high-dose single-fraction SBRT (24 Gy) versus conventionally fractionated 3DCRT (30 Gy in 10 fractions) for palliative management in untreated spinal metastases without cord compression. SBRT reduced pain levels faster during the initial 3 months after RT. Durable pain relief was achieved to a greater degree at 6 months in the SBRT group. There was no significant difference in the pattern of recorded OMED consumption between treatment arms at 3 and 6 months after RT.

Implications of available evidence

SBRT may offer quicker and more durable pain relief over a 6-month time period following therapy. SBRT has clear potential as a novel treatment approach in these patients.

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References

[1] Wong DA, Fornasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. Spine 1990;15:1–4.
[2] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243–9.
[3] Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423–36.
[4] De Bari B, Chiesa S, Filippi AR, Gambacorta MA, D'Emilio V, Murino P, et al. The INTER-ROMA project–a survey among Italian radiation oncologists on their approach to the treatment of bone metastases. Tumori 2011;97:177–84.
[5] Chow E, Hoskin P, Mitera G, Zeng L, Lutz S, Roos D, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Int J Radiat Oncol Biol Phys 2012;82:1730–7.
[6] Foro Arnalot P, Fontanals AV, Galceran JC, Lynd F, Latiesas XS, de Dios NR, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiother Oncol 2008;89:150–5.
[7] Gutierrez Bayard L, Salas Buzon Mdel C, Angulo Pain E, de Ingunza Baron L. Radiation therapy for the management of painful bone metastases: Results from a randomized trial. Rep Pract Oncol Radiother 2014;19:405–11.
[8] Kaasa S, Brenne E, Lund JA, Fayers P, Falkmer U, Holmberg M, et al. Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases. Radiother Oncol 2006;79:278–84.
[9] Katsoulakis E, Laufer I, Bilsky M, Agaram NP, Lovelock M, Yamada Y. Pathological characteristics of spine metastases treated with high-dose single-fraction stereotactic radiosurgery. Neurosurg Focus 2017;42:E7.
[10] Koswig S, Buchali A, Bohmer D, Schlenger L, Budach V. Palliative radiotherapy of bone metastases. A retrospektive analyses of 176 patients. Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft 1999;174:509–14.
[11] Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. Radiother Oncol 1998;47:233–40.
[12] Niewald M, Tkocz HJ, Abel U, Scheib T, Walter K, Nieder C, et al. Rapid course radiation therapy vs. more standard treatment: a randomized trial for bone metastases. Int J Radiat Oncol Biol Phys 1996;36:1085–9.
[13] Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. Cochrane Database Syst Rev 2004;2. CD004721.
[14] Wu JS, Wong R, Johnston M, Bezjak A, Whelan T. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. Int J Radiat Oncol Biol Phys 2003;55:594–605.
[15] Katsoulakis E, Riaz N, Cox B, Mechalakos J, Zatcky J, Bilsky M, et al. Delivering a third course of radiation to spine metastases using image-guided, intensity-modulated radiation therapy. J Neurosurg Spine 2013;18:63–8.

[16] Yamada Y, Bilsky MH, Lovelock DM, Venkatraman ES, Toner S, Johnson J, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. Int J Radiat Oncol Biol Phys 2008;71:484–90.
[17] Gestaut MM, Thawani N, Kim S, Gutti VR, Jhavar S, Deb N, et al. Single fraction spine stereotactic ablative body radiotherapy with volumetric modulated arc therapy. J Neuro-oncology 2017;133:165–72.
[18] Pokhrel D, Sood S, McClinton C, Shen X, Badkul R, Jiang H, et al. On the use of volumetric-modulated arc therapy for single-fraction thoracic vertebral metastases stereotactic body radiosurgery. Med Dosim 2017;42:69–75.
[19] Chung Y, Yoon HI, Kim JH, Nam KC, Koom WS. Is helical tomotherapy accurate and safe enough for spine stereotactic body radiotherapy? J Cancer Res Clin Oncol 2013;139:243–8.
[20] Wang XS, Rhines LD, Shiu AS, Yang JN, Selek U, Gning I, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial. Lancet Oncol 2012;13:395–402.
[21] Ryu S, Pugh SL, Gerszten PC, Yin F-F, Timmerman RD, Hitchcock YJ, et al. RTOG 0631 phase 2/3 study of image guided stereotactic radiosurgery for localized (1–3) spine metastases: Phase 2 results. Practical Radiat Oncol 2014;4:76–81.
[22] Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980;45:2220–4.
[23] Rief H, Katayama S, Bruckner T, Rieken S, Bostel T, Forster R, et al. High-dose single-fraction IMRT versus fractionated external beam radiotherapy for patients with spinal bone metastases: study protocol for a randomized controlled trial. Trials 2015;16:264.
[24] Ryu S, Pugh SL, Gerszten PC, Yin FF, Timmerman RD, Hitchcock YJ, et al. RTOG 0631 phase II/III study of image-guided stereotactic radiosurgery for localized (1–3) spine metastases: phase II results. Int J Radiat Oncol Biol Phys 2011;81:131–2.
[25] Gerszten PC, Burton SA, Quinn AE, Agarwala SS, Kirkwood JM. Radiosurgery for the treatment of spinal melanoma metastases. Stereotact Funct Neurosurg 2005;83:213–21.
[26] Nguyen QN, Shiu AS, Rhines LD, Wang H, Allen PK, Wang XS, et al. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76:1185–92.
[27] Ahmed KA, Stauder MC, Miller RC, Bauer HJ, Rose PS, Olivier KR, et al. Stereotactic body radiation therapy in spinal metastases. Int J Radiat Oncol Biol Phys 2012;82:e803–809.
[28] Moussazadeh N, Lis E, Katsoulakis E, Kahn S, Svoboda M, DiStefano NM, et al. Five-year outcomes of high-dose single-fraction spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2015;93:361–7.
[29] Jhaveri PM, Teh BS, Paulino AC, Blanco AI, Lo SS, Butler EB, et al. A dose-response relationship for time to bone pain resolution after stereotactic body radiotherapy (SBRT) for renal cell carcinoma (RCC) bony metastases. Acta oncologica (Stockholm, Sweden) 2012;51:584–8.
[30] Faruqi S, Tseng CL, Whyne C, Alghamdi M, Wilson J, Myrehaug S, et al. Vertebral compression fracture after spine stereotactic body radiation therapy: a review of the pathophysiology and risk factors. Neurosurgery 2017;18. https://doi.org/10.1093/neuros/nyx493 [Epub ahead of print].
[31] Virk MS, Han JE, Reiner AS, et al. Frequency of symptomatic vertebral body compression fractures requiring intervention following single-fraction stereotactic radiosurgery for spinal metastases. Neurosurg Focus 2017;42:E8.
[32] Rose PS, Laufer I, Boland PJ, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. J Clin Oncol 2009;27:5075–9.
[33] Boehling NS, Grosshans DR, Allen PK, et al. Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. J Neurosurg Spine 2012;16:379–86.
[34] Cunha MV, Al-Omair A, Atenafu EG, et al. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. Int J Radiat Oncol Biol Phys 2012;84:e343–349.
[35] Thibault I, Atenafu EG, Chang E, et al. Risk of vertebral compression fracture specific to osteolytic renal cell carcinoma spinal metastases after stereotactic body radiotherapy: a multi-institutional study. J Radiosurg SBRT 2015;3:297–305.